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Original Article

Epilepsy and Electroencephalographic Abnormalities in Children with Autistic Spectrum Disorder

Otistik Spektrum Bozukluğu olan Çocuk Olgularda Epilepsi ve Elektroensefalografi Anormallikleri

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ABSTRACT

Objective: Epilepsy and electroencephalography (EEG) abnormalities are more commonly seen in autism spectrum disorder (ASD). The aim of the present study is determine the risk factors that cause epilepsy, seizures and EEG abnormalities in cases with EEG examination who were followed with the diagnosis of ASD.

Method: A total of 166 cases diagnosed with ASD according to the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition in Dokuz Eylül University Faculty of Medicine Hospital Clinic of Child Psychiatry and whose neurological evaluations and examinations were performed in the pediatric neurology clinic, were included in the study. We retrospectively recorded and analyzed the cases' clinical features, the results of physical examination, imaging and EEG, comorbidities and medications they used.

Results: Of the cases, 74.4% were male. The mean age of cases with epilepsy diagnosis, at least one seizure and epileptic discharges on EEG was higher (p<0.001, p<0.001 and p=0.005, respectively). The history of epilepsy and having at least one seizure were more common in cases aged 11 years and older (p=0.001 and p=0.001, respectively). Abnormalities in EEG examination and epileptic discharges were detected to be more common in female ASD cases (p=0.041 and p=0.019 respectively).

Conclusion: In ASD cases without any underlying chronic neurological disease, female gender is a risk factor for the development of EEG abnormality and epileptic discharges. Advanced age is a risk factor for seizures and development of epilepsy in ASD cases.

Keywords: Autism, epilepsy, epileptic discharge, dysrhythmia

ÖZ

Amaç: Otistik spektrum bozukluğunda (OSB) epilepsi ve elektroensefalografi (EEG) anormallikleri daha sık görülmektedir. Biz de kliniğimizde OSB ile izlenen ve EEG incelemesi olan olgularda epilepsi, nöbet ve EEG anormallikleri varlığına neden olan risk faktörlerini belirlemek istedik.

Yöntem: Dokuz Eylül Üniversitesi Tıp Fakültesi Hastanesi Çocuk Psikiyatrisi kliniğinde Mental Bozuklukların Tanısal ve Sayımsal El Kitabı 5. Baskı'ya göre OSB tanısı almış ve çocuk nöroloji Kliniği'nde nörolojik değerlendirmesi ve EEG incelemesi yapılmış olan 166 OSB olgusunu çalışmaya dahil ettik. Retrospektif olarak olguların klinik özelliklerini, fizik muayene, görüntüleme, EEG bulgularını, eşlik eden hastalıklarını ve kullandıkları ilaçları kaydettik ve analiz ettik.

Bulgular: Olgularımızın %74,6'sı erkekti. Epilepsi tanısı olan, en az bir epileptik nöbet geçiren ve EEG'de epileptik deşarjları olan olguların yaş ortalaması daha yüksekti (p<0,001, p<0,001 ve p=0,005, sırasıyla). On bir yaş ve daha büyük olgularda epilepsi ve en az bir nöbet geçirme öyküsü daha sıktı (p=0,001 ve p=0,001 sırasıyla). EEG'de anormallik ve epileptik deşarjlar kız OSB olgularında daha sık saptandı (p=0,041 ve p=0,019 sırasıyla).

Sonuç: Altta başka bir kronik nörolojik hastalığı olmayan OSB olgularında kız cinsiyet EEG'de anormallik ve epileptik deşarjların gelişimi açısından bir risk faktörüdür. OSB olgularında ileri yaş, nöbet geçirme ve epilepsi gelişimi için bir risk faktörüdür.

Anahtar kelimeler: Otizm, epilepsi, epileptik deşarj, disritmi

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INTRODUCTION

Autistic spectrum disorder is a neurological dysfunction picture characterized by deficits in socialization and communication, causing neurodevelopmental delays and limited, repetitive behaviors [1]. The prevalence of autism spectrum disorder (ASD) today is reported to be 1 in 59 [2]. Although the prevalence of epilepsy remains stable in society, autistic spectrum disorders are increasingly being reported. Increased number of diagnosed cases may be due to the increased awareness of ASD among people and broader diagnostic criteria established in the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5), compared to the old diagnostic criteria [3].

Epilepsy prevalence in children with autism is reported as 2-46% [4,5]. Kanner's criteria formerly used in the diagnosis of autism identified severe and cognitively delayed cases. Therefore, only severe cases could be diagnosed according to Kanner's autism criteria, and the frequency of epilepsy among these cases was higher than ASD cohorts diagnosed according to DSM-5 [3,6]. In addition, it has been reported in the literature that the frequency of epilepsy in ASD cases is associated with intellectual delay, and the frequency of epilepsy is 21.5% in ASD cases with intellectual delay, and 8% in those without intellectual delay [3,4].

The prevalence of ASD in epilepsy cases was reported as 6.3%, much higher than the prevalence of 0.75-1.1% in the normal population [7]. Intellectual delay, male gender, being under 18 years of age, low age at first seizure and presence of symptomatic epilepsy, specific epilepsy syndrome (Dravet syndrome, infantile spasm, etc.) have been indicated as risk factors for the development of ASD in epilepsy cases [7]. The rate of ASD increases to 19.9% in infantile spasms, 41.9% in focal epilepsies and 47.4% in Dravet syndrome [7]. In addition, ASD is reported more frequently in Fragile X syndrome, Down syndrome, Angelman syndrome, Rett syndrome and neurocutaneous diseases than in the normal population [8]. Genetic studies have revealed that ASD, epilepsy and intellectual delay share common genetic features [8]. It has been observed that de novo mutations in ASD cases are a heterogeneous group, including copy number variants, single nucleotide polymorphisms and epigenetic variations [8]. Most of these variants have been found to be associated with synapse formation, neurotransmitter function, and neuronal plasticity [8]. As a result, there is mainly neuronal connectivity in ASD cases and neuronal excitability problems in epilepsy [8]. Thus, this epileptic activity may negatively affect neurodevelopment and cause ASD by disrupting both neuronal structure and neurotransmitter regulation [9]. Epileptiform discharges are associated with social-cognitive delay in Landau-Kleffner syndrome (LKS) or electrical status epilepticus in sleep (ESES) cases. However, the deficits observed in these cases do not fully meet the ASD criteria, and if epileptic discharges are eliminated by treatment, there may also be some improvement in this delay [3]. Atypical epilepsy and electroencephalography (EEG) abnormalities and epilepsy are detected more frequently in regressed ASD cases than in non-regressed ASD cases [10]. EEG abnormalities in ASD cases without seizure are reported in a wider range of 8-60% [11]. In addition, it has been shown that EEG abnormalities seen in ASD cases without seizure are associated with the delay of language, motor and cognitive skills during the first year of life. For this reason, children are in risk in terms of EEG abnormalities and seizure development in ASD [11,12].

MATERIALS and METHODS

The study was approved by the Dokuz Eylül University Non-Interventional Research Ethics Committee (decision no: 2017/16-11 date: 15.06.2017). It was carried out in the Pediatric Neurology Clinic of Dokuz Eylül University Medical Faculty Hospital. A total of 166 ASD patients with the age range of 2 to 17 who were diagnosed according to DSM-5 diagnostic criteria and had sleep-EEG examination were included in the study. Demographic characteristics, systemic and neurological examination findings of the cases were recorded. The cases were questioned whether there was a seizure history. The seizure type and frequency of seizures were recorded. According to International League Against Epilepsy (ILAE), epilepsy is defined as a history of having at least two non-provocative seizures and/or a seizure recurrence risk of more than 60% after one seizure [13]. We collected the data from those who had at least one seizure and among the subjects who had at least one seizure, we named those who met the definition of epilepsy by ILAE as epileptic group. The antiepileptic medications used by the cases diagnosed with epilepsy were recorded. The response of the cases to antiepileptic treatment was questioned. EEG data was recorded with Nihon Kohden 9200K brand 22-channel EEG device. The international bipolar 10-20 montage system was used. EEG data was recorded at least 30 minutes during awake and sleep periods, where arousal/awake response can also be monitored. Hyperventilation and intermittent photic stimulation

were applied. EEG examinations of the cases were re-evaluated by two pediatric neurologists. The results of EEG examination were categorized into three different groups as normal, epileptic discharge (spike, sharp wave, polyspikes, generalized spike-wave complexes), and only dysrhythmia (slow wave activity) without epileptic discharge. Cranial magnetic resonance imaging (MRI) findings were recorded. The results were statistically analyzed by using the SPSS 22.0 software. The normality distribution of the dependent variables was tested by the Kolmogorov-Smirnov test. Results were expressed as mean and standard deviation or median and 25th-75th percentiles where appropriate. The chi-square test was used to compare categorical variables. The p-value of less than 0.05 was regarded to be statistically significant.

Statistical Analysis

The results were statistically analyzed by using the SPSS 22.0 software. The normality distribution of the dependent variables was tested by the Kolmogorov-Smirnov test. Results were expressed as mean and standard deviation or median and 25th-75th percentiles where appropriate. The chi-square test was used to compare categorical variables. The p-value of less than 0.05 was regarded to be statistically significant.

RESULTS

Of the cases, 74.4% (n=124) were male and 25.3% (n=42) were female. There was no age difference between the genders (p=0.313). EEG abnormality and epileptic discharges were more common in female cases than males (p=0.041 and p=0.019, respectively). However, there was no statistical difference between females and males in terms of epilepsy and history of at least one seizure (Table 1).

Abnormalities in physical examination, MR pathologies as well as comorbidities and psychiatric diseases are given in Table 2. Concomitant comorbid conditions were present in 58.3% of the cases with abnormal physical examination and 55.5% of those with abnormality in MR (p=0.003 and p=0.052, respectively). Fourteen cases (58.3%) with abnormalities on physical examination and seven cases (38.8%) with abnormalities on MR had a psychiatric comorbidity (p=0.003 and p=1.000, respectively).

EEG abnormalities were detected in 34.3% (57/166) of our cohort, while twenty-nine (17.4%) cases had a history of at least one seizure. Twenty-five (15%) of these cases had been diagnosed with epilepsy and all were receiving antiepileptic treatment. One hundred and four (95%) of patients with normal EEG had no seizure (Figure 1). It was observed that 42.1% (24/57) of the cases with abnormal EEG had a history of at least one seizure, and 17.2% (5/29) of the cases with the history of at least one seizure had a normal EEG (p<0.001) (Table 3). Among the cases with EEG abnormalities, 64.9% (n=37) had epileptic discharge and 35.1% (n=20) had a dysrhythmia/slowing down of the ground rhythm (Figure 1). It was found that seizures and epilepsy were more commonly seen in patients with epileptic discharges on EEG (p<0.001 and <0.001, respectively) (Table 3).

The mean age of the cases who had at least one seizure was higher than those without any seizures (9.1±3.8 years vs 5.5±3.2 years respectively, p<0.001). The

Table 1. Comparision of findings of investigations in boys and girls

	Boys (n=124)		Girls (n=42)		
	n	**%**	**n**	**%**	**p**
PE abnormalities (n=24)	16	12.9	8	19	0.321
MR abnormalities (n=18)	16	12.9	2	4.7	0.129
EEG abnormalities (n=57)	37	29.8	20	47.6	**0.041**
Epileptic discharges in EEG (n=37)	22	17.7	15	35.7	**0.019**
Dysrhythmia (n=20)	15	12	5	11.9	1.000
At least one seizure (n=29)	19	15.3	10	23.8	0.241
Epilepsy diagnosis (n=25)	15	12	10	23.8	0.082
Comorbidity (n=51)	37	29.8	14	33.3	0.701
Physchiatric disorder (n=51)	40	32.2	11	26.1	0.563
Mean age (years)	6.3±3.7		5.7±3		0.313
Mean age at seizure onset	7.5±3.1		6.9±3.6		0.625

PE: Pulmonary embolism, MR: Magnetic resonance, EEG: Epilepsy and electroencephalography

mean age of the cases who were diagnosed as epilepsy were higher than non-epileptic cases (9.3±3.9 years vs 5.6±3.2 years respectively, p<0.001). The mean age of the cases detected to have epileptic discharge (7.6±3.4 years) was higher than those with dysrhythmia (5.2±2.8 years) (p=0.007). Of the cases, 86.7% (n=144) were under the age of 10 years. Among those aged 11 years or older, 45.4% had a history of epileptic seizure and 40.9% had a diagnosis of epilepsy (p=0.001 and p=0.001, respectively) (Table 3).

There were generalized EEG abnormalities in fourteen cases (24.6%) and focal EEG abnormalities in 43 (75.4%) cases. The most common focal EEG abnormalities was

Table 2. Findings of neurological examination and cranial magnetic resonance imagings and comorbidities and additional physchiatric disorders and drugs

	n	%
Abnormalities on neurological examination	**(n=24)**	**(100%)**
Dysmorphic face, minor dysmorphic changes	14	58.3
Increased DTRs, pyramidal findings	4	16.6
Movement disorders, streotypic movements	3	12.5
Hipopigmentated/hyperpigmentated skin lesions	3	12.5
Abnormalities on cranial magnetic resonance imaging studies	**(n=18)**	**(100%)**
Arachnoid cyst	4	22.2
Periventicular leukomalasia, gliotic changes	8	44.4
T2 hyperintense signal changes	4	22.2
Dilatated ventricules, decreased white matter volume, cerebral/cerebellar atrophy	2	11.1
Comorbidities	**(n=51)**	**(100%)**
Preterm/premature birth	15	29.4
Retardation on motor milestones	20	39.2
Neonatal problems (low birth weight, asphyxia)	8	15.6
Other disorders (congenital cardiac disorders, vision problems, obesity, protein-energy malnutrition)	8	15.6
Physchiatric disorders	**(n=51)**	**(100%)**
Attention deficiency and hyperactivity disorder	15	29.4
Mental retardation	5	9.8
Speech delay	31	60.7
Antiepileptic drugs	**(n=25)**	**(100%)**
Valproic acid	16	64
Carbamazepine	2	8
Valproic acid + oxcarbazepine	2	8
Valproic acid + lamotrigine	3	12
Levetiracetam	2	8
Physchiatric drugs	**(n=68)**	**(100%)**
Risperidone	38	55.8
Aripiprazole	13	19.1
Risperidone + aripiprazole	3	4.4
Methlyphenidate	8	11.7
Risperidone + aripiprazole + methlyphenidate	2	2.9
Quetiapine	2	2.9
Aripiprazole + methlyphenidate	1	1.4
Risperidone + methlyphenidate	1	1.4

DTR: Deep tendon reflexes

found to be the one originating from the frontocentral (37/43) (86%) region. Focal EEG abnormality and the detection of abnormality in the frontocentral region were not statistically related to gender, physical examination findings, and the presence of pathology at MR, presence of pathology in MRI, comorbid or accompanied psychiatric disease, coexistence of epileptic seizures and epilepsy and continuation of abnormality in the follow-up EEG. There was no statistically significant difference between physical examination findings or abnormality in MR and EEG abnormality, the presence of epileptic discharge, epileptic seizure history and diagnosis of epilepsy. Similarly, no statistically significant difference was detected in cases with EEG abnormality, those with epileptic discharge, those having a history of epileptic seizure, and those diagnosed with epilepsy in terms of comorbid conditions and additional psychiatric diseases. On the other hand, the rate of psychiatric medication use was higher in the cases with a history of epileptic seizure (p=0.039).

Twenty-five cases with a history of epileptic seizure were taking antiepileptic medication. Among those, antiepileptic response was partial in four (16%) cases. Five cases were using more than one antiepileptics. In the cohort, 68 (40.9%) cases were taking psychiatric medication, while nine of those were using more than one psychiatric medication. The rate of epileptic seizure history in the cases using more than one psychiatric medication (44.4%) was not significantly different than those using a single drug (22%) (p=0.212).

Five cases had a history of febrile convulsion. There was a family history of epilepsy in five cases, a family history of psychiatric disease in four cases, and a family history of both epilepsy and psychiatric disease in one case.

There were follow-up EEGs taken after at least 6 months in thirty-one cases (54.3%). In 20% of those with normal initial EEG, the control EEG was also found to be normal. On the other hand, an improvement was observed in the control EEG in 26.2% of those who had abnormality in their first EEG. While 50% of those with abnormality in the follow-up EEG were not taking any antiepileptic medications, 92.1% of those with a history of epileptic seizure were using at least one medication (p=0.020).

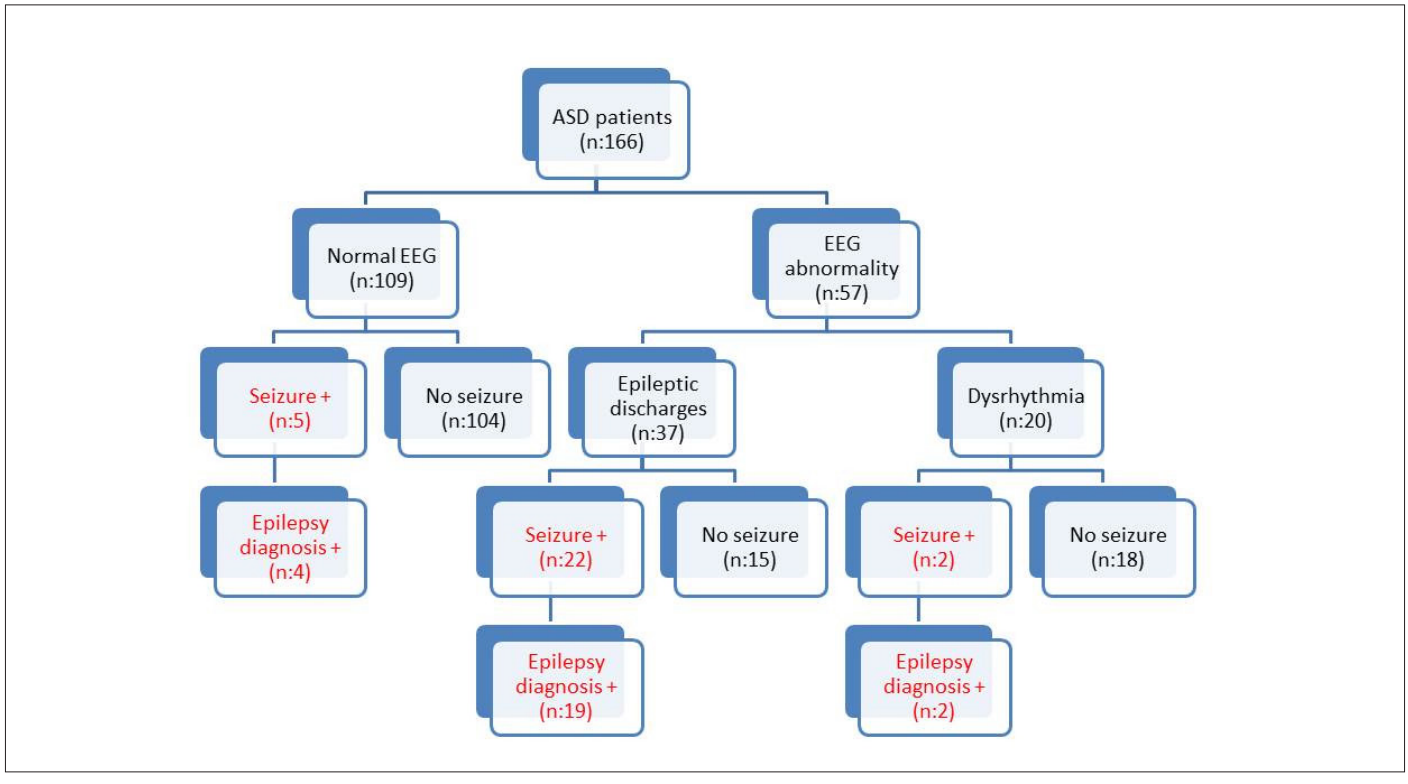

Figure 1. Flowchart of ASD patients with/without EEG abnormality and/or epilepsy

ASD: Autism spectrum disorder, EEG: Electroencephalography

Table 3. Comparision of properties of patients' groups with at least one seizure and epilepsy diagnosis						
	At least one seizure (n=29)			Epilepsy diagnosis (n=25)		
	n	%	p	n	%	p
<10 years of age (n=144)	19	13.1	**0.001**	16	11.1	**0.001**
>11 years of age (n=22)	10	45.4		9	40.9	
Abnormal EEG (n=57)	24	43.6	**<0.001**	21	36.8	**<0.001**
Normal EEG (n=109)	5	4.5		4	3.6	
ED + (n=37)	22	59.4	**<0.001**	19	51.3	**<0.001**
No ED (n=129)	7	5.4		6	4.6	
Dysrhythmia + (n=20)	2	10	0.532	2	10	0.741
No dysrhythmia (n=146)	27	18.4		23	15.7	
EEG: Electroencephalography, ED: Epileptic discharge						

DISCUSSION

In the study, we found that EEG abnormalities and especially epileptic discharges were seen more frequently in female ASD cases in our cohort. Epilepsy was detected more frequently in the cases with epileptic discharge on EEG. We observed that those diagnosed with epilepsy had a higher mean age and were followed for a longer period of time with the diagnosis of ASD. When we categorized our ASD cohort in two groups as cases under 10 years old and 11 years old or above, we detected that both groups had similar EEG abnormality rates, however, epilepsy was more frequent in the group with the age of 11 years or above. Although ASD is more frequent in males, its course is more severe in females [14]. In our cohort, 74.6% of the cases were male. In the literature, epilepsy rates in ASD cases have been reported in a wide range of 2-60%. It would be appropriate to compare our results with the studies that include cases who were diagnosed with ASD with the same diagnostic criteria, and in similar age groups. This rate differs in the range of 3.9-24.6% in studies including cases younger than 18 years of age or those defined as children [15]. However, the diagnostic criteria have not been clearly specified in all studies. While epilepsy rate has been reported to be 6.6-14.6% in studies including the cases with 0-17 age group, this rate was 24.6% in cases diagnosed with ASD in infancy and 22.5% in syndromic cases [16-20]. It was stated that the rate of epilepsy was 14.6% in the cases who were diagnosed with ASD according to the DSM-4 [16]. As can be understood from the results of the studies in the literature, epilepsy is seen much more frequently in cases diagnosed with ASD according to the diagnostic criteria applied before DSM-4 and DSM-5, in those with very early infantile onset, in those with syndromic features, and in autism cases older than 10 years of age or in adulthood [16-21]. In our study, similar to the literature, 15% of the cases were diagnosed with epilepsy, and 17.4% of the cases had seizures at least once. On the other hand, when we look at only ASD cases with the age of 11 or above in our cohort, epilepsy and experiencing at least one seizure rates increased to 45.4% and 40.9%, respectively. It was found that the mean age of the cases with epilepsy and a history of at least one seizure was also higher in our study. We included the cases who were followed up in the child psychiatry clinic with the diagnosis of ASD and applied to our child neurology outpatient clinic for EEG examination and neurological evaluation. Since our clinic is a tertiary university hospital center, we encounter more severe cases. Therefore we may have detected higher rates. Hence, the cases with ASD-like behavioral disorders who were known to have underlying severe neurological conditions such as Angelman syndrome, Rett syndrome, Dravet syndrome and West syndrome were not the subject of our study. In fact, epilepsy develops in the natural course of the disease in these cases, and the aim of our study was to detect the risk of developing epilepsy in ASD cases.

In the literature, the presence of epilepsy in ASD cases has been associated with female gender, intellectual delay, advanced age, speech problems, low socioeconomic status, and family history of ASD [3,7,21]. Although we could not find a significant difference between genders in terms of epilepsy and seizures in our study, EEG abnormalities and epileptic discharges were higher in female cases. In our cases, while concomitant attention-deficit/hyperactivity disorder and intellectual delay did not create an additional risk for epilepsy or seizures, we detected epilepsy and seizures more frequently in ASD cases with speech delay, but the difference was not statistically significant. This may be

due to the small number of cases in our cohort compared to studies and meta-analyses in which these risk factors were identified.

It has been stated in the literature that the rate of EEG abnormalities in ASD cases in the range of 8-60% [11]. On the other hand, dysrhythmic findings in EEG (asymmetry in ground rhythm, slowing, bioelectric immaturity, etc.) have been reported in various studies at different rates such as 12.5%, 13%, 21.8%, 22% and 36.8% [11,22-26]. Our cohort had EEG abnormalities in 34.3% of cases, epileptic discharges in 22.2%, and dysrhythmia in 12%. EEG abnormalities has been observed most frequently in the cases aged 5-10 years [27]. However, unlike our study, the mean age in these studies in the literature varied between 2 and 7 years. That may have been the reason we found higher mean age of the cases with epileptic discharges than those with dysrhythmia. Epilepsy and at least one seizure rates were more frequent in those who already had epileptic discharge. This situation is same with the higher mean age of those with epilepsy. EEG investigations showed abnormalities frequently on right temporal, left temporal and bitemporal regions of brain [28,29]. The right hemisphere is associated with social relationships, and the left is the region of speech. Bitemporal discharges may be related to other clinical features of ASD [29]. In another study, in which centrotemporal discharges were detected to be frequent, the population of the study was the ASD cases with seizures and regression [28]. One of the most common interictal discharges in ASD cases were those originating from the frontal regions of the brain [8]. Similarly, we also detected that the frontocentral discharges were the most frequent ones in our study. The reason for this difference from the other studies may be due to the fact that ASD cases with underlying LKS, ESES pictures or those with regression were not included in our cohort. The partial disconnectivity of the high functioning brain regions were thought to be in autism with the frontal lobe in ASD cases [30]. This may be the reason why we observed discharges in the frontocentral regions of the brain [30]. It has also been reported that epilepsy with future centrotemporal paroxysms is observed more commonly in cases with frontal EEG abnormalities [31]. Due to the small mean age of our cohort, we may have detected fewer central and temporal discharges. In a study in which 24-hour EEG recording was conducted, the rate of EEG abnormalities in ASD cases without seizures has been reported to be 60.7%. EEG abnormalities reported were spikes, sharp-wave, slow-wave, generalized spike-wave complexes, polyspikes, and paradoxical delta activity, and EEG abnormalities of all patients were shown to have occurred during sleep [28]. Detection of discharges only during sleep helps to exclude the possibility of structural defects [29]. For this reason, it is recommended to take a sleep EEG for at least 30 minutes with intermittent photic stimulation, where arousal/awake response can also be monitored [32]. Although EEG abnormalities do not cause seizure, they have adverse effects on cognition and behaviors [11]. However, in long-term follow-up, they may present with seizures, especially in adolescence period [33]. In our study, we did not find a significant difference in terms of psychiatric comorbidities in patients with EEG abnormality or epilepsy or at least one seizure compared to those without. There was a more frequent history of psychiatric medications use in those with epilepsy only.

Study Limitations

It is a limitation that we included complex cases in the study, since the study was carried out in a tertiary institution.

CONCLUSION

In summary, although ASD is more common in males, epilepsy and EEG abnormalities accompany ASD more often in females. Although EEG abnormalities are detected in ASD cases in the first decade of life, early age EEG abnormalities have a negative effect on cognitive development, and epilepsy in ASD cases begins to be seen more frequently after the age of 10. While EEG abnormalities are most frequently seen in the frontocentral, in ASD cases with epilepsy, epileptic discharges occur more commonly in bitemporal and central regions. Many genetic and environmental factors are considered among the common causes of the coexistence of ASD and epilepsy/EEG abnormalities. The detection rates of epilepsy and/or EEG abnormality in ASD cases vary greatly. It is also not yet clear how much EEG abnormality detected without seizures affects the development of epilepsy in which age group. Risk factors can be more clearly determined in studies conducted with more limited groups with well-defined and similar characteristics (gender, age group, underlying disease/genetic variant, age of onset of epilepsy, age of onset of ASD findings, etc.).

Ethics

Ethics Committee Approval: The study was approved by the Dokuz Eylül University Non-Interventional Research Ethics Committee (desicion no: 2017/16-11 date: 15.06.2017).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Author Contributions

Surgical and Medical Practices: İ.P., A.S.H., U.Y., M.A., D.O., E.B., H.B.B., Concept: İ.P., A.S.H., U.Y., M.A., D.O., E.B., H.B.B., Design: İ.P., A.S.H., U.Y., M.A., D.O., E.B., H.B.B., Data Collection and/or Processing: İ.P., A.S.H., U.Y., M.A., D.O., E.B., H.B.B., Analysis and/or Interpretation: İ.P., A.S.H., U.Y., M.A., D.O., E.B., H.B.B., Literature Search: İ.P., A.S.H., U.Y., M.A., D.O., E.B., H.B.B., Writing: İ.P.

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